EXHIBIT 6

48 FR 54983-02, 1983 WL 171904(F.R.)
PROPOSED RULES
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
21 CFR Parts 182 and 184
[Docket No. 77N–0034]

GRAS Status of Licorice (Glycyrrhiza), Ammoniated Glycyrrhizin, and Monoammonium Glycyrrhizinate

Thursday, December 8, 1983

***54983** AGENCY: Food and Drug Administration.

ACTION: Tentative final rule.

SUMMARY: The Food and Drug Administration (FDA) is tentatively affirming that licorice (glycyrrhiza), ammoniated glycyrrhizin, and monoammonium glycyrrhizinate are generally recognized as safe (GRAS), with specific limitations, as flavoring agents, flavor enhancers, and surfactants for use in human food except when used as sugar substitutes. The safety of these ingredients has been evaluated under the comprehensive safety review conducted by the agency. FDA is publishing this document as a tentative final rule to permit comments on the revised method of analysis for glycyrrhetic acid; the provision for interchangeable use of licorice, licorice extract, ammoniated glycyrrhizin, and monoammonium glycyrrhizinate; and the revised conditions of use for these ingredients.

DATE: Comments by February 6, 1984.

ADDRESS: Written comments may be sent to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Vivian Prunier, Bureau of Foods (HFF–335), Food and Drug Administration, 200 C St. SW., Washington, DC 20204; 202–426–5487.

SUPPLEMENTARY INFORMATION: In the Federal Register of August 2, 1977 (42 FR 39117), FDA published a proposal to affirm that licorice (glycyrrhiza) and ammoniated glycyrrhizin are GRAS for use as direct human food ingredients, with specific limitations. In the Federal Register of May 15, 1979 (44 FR 28334), FDA proposed that ammoniated glycyrrhizin be used only as a licorice flavor in specific foods or as a surfactant in nonalcoholic beverages. The proposals were published in accordance with the announced FDA review of the safety of GRAS and prior-sanctioned food ingredients.

In accordance with § 170.35 (21 CFR 170.35), copies of the scientific literature review on glycyrrhiza, teratogenicity and mutagenicity tests on ammoniated glycyrrhizin, and the report of the Select Committee on GRAS Substances (the Select Committee) on licorice, glycyrrhiza, and ammoniated glycyrrhizin have been made available to the public at the Dockets Management Branch (address above). Copies of these documents have also been made available for public purchase from the National Technical Information Service, as announced in the August 2, 1977 proposal.

In addition to proposing to affirm the GRAS status of licorice and ammoniated glycyrrhizin, FDA gave public notice in the August 2, 1977 proposal that it was unaware of any prior-sanctioned food ingredient use for these substances, other than for the proposed conditions of use. Persons asserting additional or extended uses, in accordance with approvals granted by the U.S. Department of Agriculture or FDA before September 6, 1958, were given notice to submit proof of those sanctions, so that the safety of the prior-sanctioned uses could be determined. That notice was also an opportunity to have prior-sanctioned uses

of licorice and ammoniated glycyrrhizin recognized by issuance of an appropriate final rule under Part 181—Prior-Sanctioned Food Ingredients (21 CFR Part 181) or affirmed as GRAS under Part 184 or 186 (21 CFR Part 184 or 186), as appropriate.

FDA also gave notice that failure to submit proof of an applicable prior sanction in response to the proposal would constitute a waiver of the right to assert such sanction at any future time.

No reports of prior-sanctioned uses for licorice or ammoniated glycyrrhizin were submitted in response to the proposal. Therefore, in accordance with the proposal, any right to assert a prior sanction for the use of these ingredients under conditions different from those set forth in this tentative final rule has been waived.

After publication of the proposal, the agency received reports of two mutagenicity studies: A dominant lethal test in rats (Ref. 1) and a test for unscheduled DNA synthesis in mice (Ref. 2). Both tests were negative.

In response to comments, which are discussed in detail below, FDA is proposing to establish specific limitations on glycyrrhizin content rather than to establish such limitations for each form of licorice. Because glycyrrhizin is the substance in the various forms of licorice that may cause transient hypertensive effects when it is consumed in large doses (see the Select Committee report on licorice and glycyrrhizin and paragraphs 7 and 8 below), it is the glycyrrhizin content that appropriately is subject to specific limitation.

Glycyrrhizin gives licorice its characteristic flavor and is present in licorice root, block licorice extract, licorice extract power, and other licorice preparations at varying levels depending upon the moisture content and processing of the ingredient. Data on the glycyrrhizin levels in typical preparations of licorice that are commercially available were submitted as comments on the proposals. Using this information, FDA has calculated the amount of glycyrrhizin that would occur in food when licorice is used at the levels that were set forth in the proposals or were reported as comments ***54984** on the proposals. The establishment of specific limitataions on the ghlycyrrhizin content in food will permit licorice root, block licorice extract, licorice extract powder, and ammoniated glycyrrhizin to be used interchangeably or in any combination in food.

FDA received nine comments on the August 2, 1977 proposal and nine comments on the May 15, 1979 amended proposal. A summary of the comments and the agency's conclusions follows:

1. Three comments said that licorice extract powder is prepared by spray-drying licorice extract, not by grinding the concentrated extract solids as stated in proposed § 184.1408a)(1) (21 CFR 184.1408(a)(1)). One comment reported that licorice extract is commercially available as a liquid, in addition to the paste (“block” licorice) and powder described in the proposal.

The agency has revised § 184.1408(a)(1) to reflect this information.

2. Two comments said that proposed § 184.1408(b) (§ 184.1408(a)(2) in this tentative final rule) gives the formula for monoammonium glycyrrhizinate while describing a manufacturing method for ammoniated glycyrrhizin. The comments requested that FDA revise the proposed regulation to make clear that it covers both ammoniated glycyrrhizin and the more highly purified monoammonium glycyrrhizinate. The comments said that the description of the manufacturing process of ammoniated glycyrrhizin should also be changed to reflect actual practices.

Monoammonium glycyrrhizinate is a highly purified form of ammoniated glycyrrhizin. The agency agrees that the proposed regulation should covers this substance and has revised the tentative final rule to include monoammonium glycyrrhizinate. Unless otherwise indicated, throughout this preamble, FDA will use the term “ammoniated glycyrrhizin” to refer to both ammoniated glycyrrhizin and monoammonium glycyrrhizinate. The agency has also revised the description of the manufacturing process of ammoniated glycyrrhizin in accordance with the suggestions made in the comments.

3. Two comments said that the procedure given for the analysis of the glycyrrhizin content of licorice and ammoniated glycyrrhizin is obsolete. One comment suggested that a high-pressure liquid chromatography method be substituted.

The agency agrees that the analytical method for glycyrrhizin should reflect current technology. In the "Official Methods of Analysis," 13th Ed., the Association of Official Analytical Chemists (AOAC) validated a gas chromatographic method for ammonium glycyrrhizinate, which is measured as glycyrrhetic acid, a derivative of glycyrrhizin. This procedure is more sensitive than the one previously proposed. Therefore, the agency has modified the regulation to incorporate this procedure. The high-pressure liquid chromatography method mentioned in the comment has not been published and has not been validated by the AOAC. Thus, it is appropriate to incorporate it into the regulation. When the method has been validated, the agency will consider the need to adopt the new method and will propose to amend the regulation if that action is indicated.

The 1977 proposal required that the glycyrrhizin content of the ingredient be within the range specified by the vendor. FDA finds, however, that the question whether the actual glycyrrhizin content of the ingredient conforms with the stated glycyrrhizin content is an issue of economics and not safety. FDA has therefore concluded that vendor specifications are not relevant for compliance with this tentative final rule. Accordingly, the agency is deleting the requirement of vendor specifications for glycyrrhizin content of the ingredient.

4. One comment requested modification of the specifications for licorice to permit an ash content that does not exceed 9.5 percent on an anhydrous basis. The comment said that the ash content of the finished product varies with the geographic origin of the licorice root and ranges from 6.5 to 9.5 percent. The comment also suggested that the specifications should be modified to permit not more than 2.5 percent ash for ammoniated glycyrrhizin and not more than 0.5 percent for monoammonium glycyrrhizinate on an anhydrous basis.

The agency agrees that the proposed regulation should describe the ingredients that are used in commerce and has revised the specifications for ash contents in accordance with this comment.

5. Three comments on the 1977 proposal asked that the use levels of the various forms of licorice (root, block extract, and powdered extract) be proportional to their glycyrrhizin content. The comments provided data on the glycyrrhizin content of licorice root, block extract, and powdered extract. These data indicated that licorice root (moisture content of 4.5 percent) contains 11.8 percent glycyrrhizin by weight, block licorice extract (moisture contents of 22.4 percent) contains 19.5 percent glycyrrhizin by weight, and licorice extract powder (moisture content of 5.2 percent) contains 23.7 percent glycyrrhizin by weight. Other comments asked that the agency establish a maximum glycyrrhizin level for each food category instead of specifying maximum levels for each form of licorice in each food. Under these suggestions, the various forms of licorice could be used in any combination, provided that the total amount of glycyrrhizin in the food did not exceed the maximum established for that food category.

The agency agrees that this tentative final rule should be modified to establish maximum glycyrrhizin levels in food. This modification will permit the interchangeable use of licorice root, block licorice extract, and licorice extract powder that was requested in these comments and the interchangeable use of the various forms of licorice and ammoniated glycyrrhizin that was requested in the comments discussed in paragraph 14 below. Under this provision, the various forms of licorice or ammoniated glycyrrhizin may be used in any combination, provided that the glycyrrhizin content does not exceed the maximum glycyrrhizin level specified for the food.

The agency finds that there are three reasons for making this change. Glycyrrhizin, which is the characterizing flavoring substance of licorice, has the potential to cause transient hypertensive effects when it is consumed in large doses (see the Select Committee report on licorice and glycyrrhizin and paragraphs 7 and 8 below). Therefore, it is appropriate to limit specifically consumer exposure to glycyrrhizin. Secondly, it is not possible to distinguish glycyrrhizin derived from licorice root or licorice extract from glycyrrhizin derived from ammoniated glycyrrhizin. Thirdly, this change will afford food manufacturers maximum flexibility, within the specific limitations established in this tentative final rule, in formulating food that contains licorice or

ammoniated glycyrrhizin. Accordingly, the agency is no longer specifying use levels for the individual forms of licorice or for ammoniated glycyrrhizin in each food but is establishing maximum glycyrrhizin levels that can occur in each food category as the result of the GRAS uses of these ingredients.

The data supplied in the comments on the glycyrrhizin contents of the various forms of licorice have allowed the agency to calculate the amount of glycyrrhizin that would occur in food when typical commercial preparations of licorice root, licorice extract, or ***54985** ammoniated glycyrrhizin are used at the proposed levels or at levels reported in comments. In calculating these glycyrrhizin levels, the agency considered the practice, reported in comments, of using a combination of two or more forms of licorice in some foods. The agency had interpreted the use information in the 1971 National Academy of Sciences/ National Research Council (NAS/NRC) survey of industry on the use of GRAS substances to mean that only one form of licorice was added to a particular food. However, the agency has learned from the comments that the practice was otherwise. Thus, the maximum glycyrrhizin content of foods, which is discussed for specific foods in the paragraphs below, is based upon the calculation of the glycyrrhizin level that would result when the licorice ingredients are used in combination at the maximum reported levels.

6. Two comments on the 1977 proposal requested adjustments in the use levels of licorice root and licorice extract in soft and hard candies. One comment submitted data showing that under current good manufacturing practice (CGMP), soft candy may contain up to 1.0 percent licorice root by weight in the finished food, 5.6 percent licorice block extract, and 8.0 percent licorice extract powder. As interpreted by the comment, the 1977 proposal would have permitted the use of these ingredients in any combination up to the maximum levels for each form of licorice. The use of licorice ingredients in combination at the levels reported in the comment wdould result in a maximum glycyrrhizin level of 3.1 percent in soft candy (see paragraph 5 above for a discussion of the glycyrrhizin content of licorice ingredients). The other comment stated that the proposed use levels for licorice ingredients in hard candy do not include a particular type of licorice food product, even if all forms of licorice were used in combination at the maximum levels. The comment described the product as being composed almost entirely of licorice and having a serving size of 0.1 ounce. The comment stated that the product has been sold in the United States for at least 30 years. The comment requested that the use levels of licorice extract powder in hard candy be raised to 24 percent. The use of licorice ingredients at the levels requested in this comment would result in a glycyrrhizin content of 16 percent in hard candy.

The agency agrees that the specific use limitations of licorice ingredients in soft and hard candies should reflect CGMP, provided that these levels do not result in a significant increase in the consumption of glycyrrhizin. The agency has evaluated the use levels requested in the comments and has found that the use of licorice ingredients at the reported levels in soft and hard candies would not result in a significant increase in the consumption of glycyrrhizin. Accordingly, the agency has modified the proposed regulation to accommodate the use of licorice in hard and soft candies as reported in the comments. Proposed § 184.1408 would permit the use of licorice root and extracts, singly or in any combination, at levels that result in glycyrrhizin levels that do not exceed 3.1 percent in soft candy and 16 percent in hard candy.

7. One comment reported an instance of acute severe hypertension resulting from the consumption of licorice tea. The comment requested that the agency take action to reduce the potential hazard that licorice presents to the public and included several published reports of licorice toxicity to support the request.

The agency has reviewed the reports submitted in the comment as well as other data that have become available since the publication of the Select Committee report. These data (Refs. 3 through 9) include several reports of human toxicity following chronic consumption of high levels of licorice and one report of licorice-induced pseudoprimary aldosteronism elicited experimentally in normal human subjects. However, FDA was aware, even before it received these reports, that these types of toxicity have been associated with ingestion of licorice. For example, in its report, the Select Committee noted the capacity of high doses of glycyrrhizin from licorice and its derivatives to elicit transient hypertensive effects. Additionally, some of the new data indicate that some individuals may be sensitive even to low levels of glycyrrhizin, and that the hypertensive effects of glycyrrhizin may be of concern to persons with hypertensive or circulatory disease.

FDA finds that the adverse effects of glycyrrhizin are generally associated with the consumption of foods that are characterized by a distinctive licorice flavor, such as licorice-flavored candies, liqueurs, or other beverages. These foods contain higher levels of glycyrrhizin than do foods in which the licorice or ammoniated glycyrrhizin has been added as a flavor enhancer. Persons who are sensitive to glycyrrhizin can avoid experiencing glycyrrhizin-induced symptoms by excluding licorice-flavored foods from their diets. FDA believes that the levels of glycyrrhizin contained in foods do not pose a hazard to the public, provided that foods that contain glycyrrhizin are not consumed in excessive quantities or by individuals who are sensitive to low levels of glycyrrhizin.

The new data underscore the need to limit the consumption of glycyrrhizin but do not indicate a need to change its status as a GRAS ingredient. The agency does not have any specific data that indicate how many people consume large quantities of products that contain high levels of glycyrrhizin and, consequently, might be at risk of developing adverse effects from this chemical. From the consumption data that are available, however, the agency estimates that the number of consumers in this group is likely to be insignificant compared to the total population. Thus, the agency concludes that the available information establishes that specific limitations on the use of licorice and ammoniated glycyrrhizin in food are appropriate, but that no further change in the regulatory status of these ingredients is warranted.

The reported use of licorice in licorice tea raises the issue of the status of this use of the ingredient. The use of licorice to make tea is not authorized by § 182.10 Spices and other natural seasonings and flavorings (21 CFR 182.10) and was not proposed for GRAS affirmation in proposed § 184.1408. Because no manufacturer of licorice tea has provided any use information on these products as comments on the proposals, the agency is not able to evaluate the safety of this use. Consequently, the agency is not able to conclude that this use is GRAS.

8. Three comments on the 1979 proposal asserted that the safety data did not indicate the need for the proposed specific limitations included in the regulation. Two of these comments included safety data to support this claim.

The safety data that were submitted included a literature review on the toxicological effects of ammoniated glycyrrhizin; oral LD50 studies in the mouse, rat, and guinea pig; an 8-week oral study in the rat; 16-week studies in the rat and mouse; and a series of special studies intended to test corticomimetic activity of ammoniated glycyrrhizin in the rat (Refs. 10 and 11). No adverse effects were noted at doses of up to 700 milligrams per kilogram in the 8-week study or 90 milligrams per kilogram in the 16-week studies.

The agency finds that these reports do not include any long-term studies in either animals or humans. The agency would require data on chronic exposure ***54986** to glycyrrhizin before it could conclude that unlimited use of ammoniated glycyrrhizin is safe.

The agency concludes that the available data, including the data submitted as comments, are not sufficient to evaluate the safety of significantly increased consumption of glycyrrhizin that would result from expanded uses of ammoniated glycyrrhizin or of licorice. Therefore, FDA believes that the submitted data do not obviate the need for specific limitations on the use of the ingredients. (See also the agency's response to comment 7.)

9. Several comments on the 1979 proposal argued that the proposed specific limitations are unnecessary because the use of ammoniated glycyrrhizin is self-limiting for various reasons. These comments pointed out that the amount of ammoniated glycyrrhizin that can be used to achieve nonlicorice flavor in food is limited by the licorice flavor of the ingredient, which breaks through at higher levels, marring the intended subtle flavoring effect. Another comment stated that the usefulness of monoammoniated glycyrrhizinate is further limited because it is nearly insoluble in cold water, and because when added to hot water, it forms a gel upon cooling. Other comments said that declining availability of licorice root should obviate any concern about increased consumption of ammoniated glycyrrhizin.

The agency finds that the technological factors described in the comments indicate that the level of ammoniated glycyrrhizin and monoammoniated glycyrrhizinate in food will be self-limiting in many food applications. However, as suggested by U.S.

patent 3,851,073 (a copy of which was submitted in a comment), which describes the use of a 5′-nucleotide flavor enhancer to suppress the licorice flavor of ammoniated glycyrrhizin, techniques can be developed to overcome existing technological limitations. The agency believes that new technology might allow new uses of these ingredients and thus result in an increase in consumption. Therefore, although technological limitations reinforce limits set for safety reasons, they do not eliminate the need for establishing those limits.

In regard to the limited availability of licorice root, the data submitted indicate that the tobacco industry uses 90 percent of the U.S. supply of licorice root, and that the food and pharmaceutical industries each use 5 percent of the supply of licorice root. These data also show that the use of ammoniated glycyrrhizin in food currently accounts for 2 percent of the U.S. supply of licorice root. Although FDA agrees that the availability of licorice root is diminishing, it is possible that future economic conditions or market forces will divert a greater portion of the supply of licorice root to the production of ammoniated glycyrrhizin for food use. In this event, consumption of ammoniated glycyrrhizin could increase above current levels. Consequently, specific limitations are required.

10. Several comments stated that the 1979 proposal, which stipulated that ammoniated glycyrrhizin is to be used only to produce licorice flavor, is not consistent with the Select Committee's report. Additionally, the comments contended that the 1979 proposal is overly restrictive and would not permit traditional uses of the ingredient. To support these statements the comments argued that the description of the sweetness and flavor-enhancing effects of the ingredient that appeared in the preamble of the 1977 proposal constitute agency recognition of these uses. The comments interpreted a statement in the Select Committee report that ammoniated glycyrrhizin has been important to the food industry because of its sweetness as recognition that extant uses of the ingredient as a sweetening agent were considered by the Select Committee in its review. One comment also pointed out that the 1971 NAS/NRC survey of food manufacturers reported that the ingredient is used to formulate a variety of nonlicorice flavors such as “fermented,” “fruit-pulpy,” “root,” “vanilla,” and “cooked, brown and roasted” (e.g., caramel, cocoa, or maple).

Other data submitted in the comments show that ammoniated glycyrrhizin has been used for its sweetness and sweetness-potentiating effects since the 1940's, when the ingredient was added to cough syrup to mask the bitter taste of the medicine. These data also show that in the 1940's, there was a practice of using ammoniated glycyrrhizin in beverages, including root beer. Other pre-1958 uses of the ingredient, according to these data, included its use in chocolate, in chewing gum, and in many nonlicorice flavorings that were added to a variety of foods. Thus, the submitted data demonstrate that ammoniated glycyrrhizin was used in the United States to enhance nonlicorice flavors before 1958.

In the May 15, 1979 proposal, the agency stated that it would consider reinstating the nonlicorice flavoring uses of ammoniated glycyrrhizin originally included in the August 2, 1977 proposal if data were submitted that evidenced a history of prior use. The agency has considered the comments and has reexamined the record used to support this rulemaking. The record does indeed show that ammoniated glycyrrhizin was used before 1958, and that it is currently used as a flavor enhancer and sweetness enhancer. Moreover, the record shows that these uses were considered by the Select Committee in its review. The agency tentatively concludes that these uses are indeed GRAS because there are adequate data to support that these historic and ongoing uses are safe. Accordingly, FDA is no longer specifying that ammoniated glycyrrhizin be used as a licorice flavor only. Proposed § 184.1408 would permit the use of the ingredient as a flavoring agent (21 CFR 170.3(o)(12)) and flavor enhancer (21 CFR 170.3(o)(11)).

FDA has considered the need to establish a listing in the proposed regulation for the sweetness-enhancing function of ammoniated glycyrrhizin and, to reflect this function, has considered including the technical effect of “synergist” (21 CFR 170.3(o)(31)) in the GRAS affirmation regulation. The agency finds, however, that in the GRAS uses reported in the comments discussed above, the ingredient is used not only as a sweetness enhancer but also as a flavor enhancer. FDA concludes that listing the flavoring agent and flavor enhancer uses of the ingredient will provide for the current sweetness-enhancing uses of ammoniated glycyrrhizin, and that it is therefore not necessary to include “synergist” in the list of the functional uses in the regulation.

11. Two comments on the 1977 proposal reported that ammoniated glycyrrhizin could be used as a nonnutritive sweetener in sugar substitute products and inquired whether this use would be covered by the proposal.

After publication of the 1977 proposal, FDA learned that ammoniated glycyrrhizin was actually being used as a nonnutritive sweetener in a saccharin-free sugar substitute. Because none of the comments on the 1977 proposal were from manufacturers of this product, the agency did not have data showing the use level of ammoniated glycyrrhizin in this food. Therefore, the agency was unable to determine the extent to which consumer exposure to glycyrrhizin would be increased as a result of this new use of ammoniated glycyrrhizin. In the absence of consumer exposure information, the agency was not able to evaluate the safety of this use, and, as a result, in 1979, FDA proposed not to ***54987** affirm this use as GRAS. No information on this use was supplied in the comments on the 1979 proposal.

On the basis of the Select Committee's opinion and the agency's own evaluation of the toxicity data, FDA has tentatively concluded that new uses of ammoniated glycyrrhizin, such as its use as a sugar substitute, should not be affirmed as GRAS until additional toxicity studies are conducted. Consequently, FDA is excluding the use of ammoniated glycyrrhizin as a sugar substitute as defined in § 170.3(n)(42) (21 CFR 170.3(n)(42)) from this GRAS affirmation regulation.

12. Several comments reported current uses of ammoniated glycyrrhizin that were not included in the 1979 proposal, and uses of this substance in which the levels of ammoniated glycyrrhizin added to food have increased above those reported in the proposal. The comments show that use of ammoniated glycyrrhizin in accordance with CGMP as a flavor in nonalcoholic beverages results in a level of 0.15 percent ammoniated glycyrrhizin in the food rather than 0.01 percent as proposed. The comments also show that the use of the ingredient in accordance with CGMP in both alcoholic and nonalcoholic beverages as a foam stabilizer results in levels of 0.1 percent ammoniated glycyrrhizin in the food rather than 0.002 percent in nonalcoholic beverages as proposed. According to other comments, the CGMP use of the ingredient as a flavoring agent or flavor enhancer results in levels of 0.1 percent in confections and frostings and sweet sauces and 0.15 percent in herbs and seasonings and in reconstituted vegetable proteins.

Other comments reported uses of the ingredient, which began after the 1971 NAS/NRC survey, in foods that contain low-calorie sweeteners. According to these comments, ammoniated glycyrrhizin has been used since 1970, at levels not exceeding 0.1 percent, to mask the bitter aftertaste of saccharin in diet cola. The comments also reported that since 1976 the ingredient has been added to low-calorie ice cream with sorbitol at 0.003 percent as a sweetener enhancer, and that it is also used as a sweetener enhancer in gelatin and pudding at a level of 0.036 percent.

FDA finds that the uses of ammoniated glycyrrhizin reported in these comments, as a foam stabilizer in beverages and as a flavor or as a flavor enhancer in confections and frostings, sweet sauces, herbs and seasonings, and reconstituted vegetable proteins, are consistent with the uses of this ingredient that predate the 1958 amendments and that were evaluated by the Select Committee. The comments provide data to show that the new uses would not result in significant increases in the consumer exposure to ammoniated glycyrrhizin. FDA finds that there is sufficient published safety information to support these uses and that the functional use as a foam stabilizer in both alcoholic and nonalcoholic beverages is covered by the term “surface-active agent” under § 170.3(o)(29). Accordingly, the agency has tentatively concluded that these new uses are GRAS.

FDA also finds that the use of ammoniated glycyrrhizin as a sweetener enhancer in combination with low-calorie sweeteners is analogous to its function as a sweetener enhancer in combination with nutritive sweeteners. Although this use of the ingredient also is new and was not considered by the Select Committee, the comments provide sufficient data to permit an agency determination that this use will not result in a significant increase in consumer exposure to ammoniated glycyrrhizin. Because there is also adequate published information to establish the safety of this use, the agency has tentatively concluded that this use of the ingredient is GRAS.

In accordance with the foregoing, the agency has tentatively decided to affirm as GRAS the use of the ingredient as a flavoring agent, flavor enhancer, and surface-active agent in nonalcoholic beverages at a use level of 0.15 percent and in alcoholic

beverages at a use level of 0.1 percent. This tentative final rule also proposes to affirm as GRAS the use of the ingredient as a flavoring agent and flavor enhancer in herbs and seasonings and reconstituted vegetable proteins at use levels of 0.15 percent and in confections and frostings, sweet sauces, gelatins and puddings, and frozen dairy desserts at levels of 0.10 percent. The latter uses are included in the "all other foods" listings.

13. Two comments on the 1979 proposal requested GRAS affirmation of ammoniated glycyrrhizin when used as a flavoring agent in vitamin or mineral dietary supplements, e.g., vitamin tablets, at levels up to 0.5 percent.

Ordinarily, FDA does not affirm as GRAS the use of an ingredient in dietary supplements because the agency lacks consumer exposure data for these products. In this case, however, the Select Committee considered reports describing the use of licorice and ammoniated glycyrrhizin in dietary supplements. The Select Committee used these data in reaching its conclusion on the safety of current uses of these ingredients. Therefore, the agency agrees that the use of these ingredients as flavorings in vitamin or mineral dietary supplements may be affirmed as GRAS with specific limitations up to the level requested. FDA has modified the tentative final rule to reflect this use.

14. Six of the nine comments on the 1979 proposal on ammoniated glycyrrhizin asked that FDA adopt either the entire 1977 proposal or permit ammoniated glycyrrhizin to be used at the 0.17 percent use level in "all other foods," as the agency had proposed to do in the 1977 document. One comment suggested that FDA permit ammoniated glycyrrhizin to be used at a level of 0.1 percent in "all other foods." Two comments asserted that the 1979 proposal would restrict the current practice of substituting ammoniated glycyrrhizin for cruder forms of licorice because it permits ammoniated glycyrrhizin to be added only to specific foods rather than "all other foods." The comment pointed out that, in contrast, the 1977 proposal would have permitted both licorice and ammoniated glycyrrhizin to be used in "all other foods." According to the comments, the use of ammoniated glycyrrhizin instead of licorice results in a lower level of glycyrrhizin in the finished food. To permit this substitution, the comments requested the establishment of a use level for ammoniated glycyrrhizin in "all other foods."

FDA agrees that the regulation should be modified to permit licorice and ammoniated glycyrrhizin to be used interchangeably (as discussed in paragraph 5 above). To provide for this interchangeable use, the agency is proposing to affirm as GRAS the use of glycyrrhizin in "all other foods," regardless of the source of the glycyrrhizin. Because the agency lacks consumption data on the use of ammoniated glycyrrhizin in sugar substitutes (21 CFR 170.3(n)(42)), however, the proposed regulation specifically excepts sugar substitutes from the "all other foods" category (see paragraph 11 above).

FDA finds that the maximum glycyrrhizin level in "all other foods" should be set at a level that is high enough to accommodate interchangeable use of licorice and ammoniate glycyrrhizin, as requested in the comment, but not so high that use of the ingredient in "all other foods" results in a significant increase in the consumption of glycyrrhizin. The 1977 proposal on licorice would have permitted licorice root to be used at a level of 0.07 percent in "all other foods" and licorice extract powder and licorice block extract to be used in "all other ***54988** foods" at levels of 0.04 percent and 0.17 percent, respectively. Using the data on the glycyrrhizin content of licorice (see paragraph 5 above) and assuming that the ingredients may be used in combination in a food, FDA has calculated that the use of licorice in accordance with the 1977 proposal would have resulted in a glycyrrhizin content of 0.06 percent in "all other foods."

Comments on the 1979 proposal show that ammoniated glycyrrhizin is used at a level of 0.15 percent or higher in relatively few foods, and that use of this ingredient at a level of 0.1 percent is sufficient to achieve the desired effect in most foods.

The agency finds that the submitted use information does not support the establishment of a maximum glycyrrhizin level in "all other foods" at a level of 0.17 percent as requested by the comments. The agency is concerned that establishment of a maximum glycyrrhizin level of 0.17 percent in "all other foods" would permit new uses of licorice or ammoniated glycyrrhizin that could result in increased consumption of glycyrrhizin. The agency concludes that establishment of a maximum glycyrrhizin level of 0.1 percent in "all other foods" would permit all the uses of ammoniated glycyrrhizin reported in the comments on the 1979 proposal (except its use as a sugar substitute), all uses of licorice proposed in the 1977 proposal, and also the interchangeable use of the

various forms of licorice and ammoniated glycyrrhizin. Accordingly, the tentative final rule specifies foods in which the use of licorice or ammoniated glycyrrhizin results in a glycyrrhizin content of 0.15 percent or higher and permits these ingredients to be used in any other food not specifically listed at levels that result in a glycyrrhizin content of 0.1 percent. However, the tentative final rule also establishes a maximum glycyrrhizin content of 0.05 in baked goods. The glycyrrhizin content for baked goods is lower than that for "all other foods" because FDA has no data to show that licorice or ammoniated glycyrrhizin is used at levels which would result in a higher glycyrrhizin content in this food category. These actions are consistent with FDA's intent to limit exposure to glycyrrhizin contained in licorice or ammoniated glycyrrhizin to current levels.

15. Several comments inquired about the status of the uses of ammoniated glycyrrhizin that may be developed after FDA publishes the results of its safety review. In addition, a comment on the 1979 proposal stated that new products had been developed on the basis of the level originally proposed of 0.17 percent in "all other foods."

As discussed in paragraph 14 above, this tentative final rule affirms the use of ammoniated glycyrrhizin in "all other foods" at a level of 0.1 percent rather than 0.17 percent. This provision may not cover the newly developed products alluded to in the comment because FDA does not have information about these new uses. Interested persons may comment on current uses that are excluded by this tentative final rule. The agency will determine whether these uses significantly add to the exposure to glycyrrhizin. Comments on the uses of these ingredients should provide specific information on levels of use, food categories, and technical effects. Alternatively, persons seeking FDA approval of these uses may submit a GRAS affirmation petition or a food additive petition in accordance with §§ 170.35 and 171.1.

16. Two comments said that the promulgation of the amended proposal would cause economic damage because it would eliminate virtually the entire market for ammoniated glycyrrhizin.

As indicated above, FDA has modified this tentative final rule from the 1979 proposal to include additional uses of ammoniated glycyrrhizin that the agency has tentatively determined to be GRAS. FDA believes that the tentative final rule consequently will not adversely affect the market for this ingredient, and that it will not cause the economic damage forecast in the comment.

In summary, this tentative final rule differs from the previous proposals as follows:

1. It incorporates a gas chromatographic assay for glycyrrhizin, measured as glycyrrhetic acid, in place of the previously proposed spectrophotometric method;

2. It includes additional technical effects for the ingredients;

3. It permits interchangeable use of licorice and ammoniated glycyrrhizin.

4. It sets limits on total glycyrrhizin content of food, regardless of source, instead of limiting the use level of each ingredient, as previously proposed.

5. It permits licorice and ammoniated glycyrrhizin to be used in more foods, establishes higher use levels than previously proposed, and restores the provision for the use of ammoniated glycyrrhizin in all other foods. The tentative final rule would establish maximum glycyrrhizin levels in food as a flavoring agent or flavor enhancer as follows: 0.05 percent in baked goods; 1.1 percent in chewing gum; 16 percent in hard candy; 0.15 percent in herbs and seasonings; 0.15 percent in plant protein products; 3.1 percent in soft candy; 0.5 percent in vitamin or mineral dietary supplements; and 0.1 percent in all other foods except sugar substitutes. The tentative final rule also would establish maximum glycyrrhizin levels of 0.1 percent in alcoholic beverages and 0.15 percent in nonalcoholic beverages as a surface-active agent as well as flavoring agent or flavor enhancer.

In order to afford interested persons the opportunity to comment on these changes, FDA is issuing this tentative final rule under § 10.40(f)(6) (21 CFR 10.40(f)(6)). FDA will review any comments relevant to these changes that it receives within the 60-day

comment period and will issue in the Federal Register either an announcement that this tentative final rule has become final or an announcement of modification to this regulation made on the basis of new comments.

The agency has determined under 21 CFR 25.24(d)(6) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

FDA, in accordance with the Regulatory Flexibility Act, has considered the effect that this tentative final rule would have on small entities including small businesses. Because the tentative final rule affirms all known current uses of the ingredients, FDA certifies in accordance with section 605(b) of the Regulatory Flexibility Act that no significant economic impact on a substantial number of small entities will derive from this action.

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this tentative final rule, and the agency has determined that the final rule, if promulgated from this tentative final rule, would not be a major rule as defined by the Order.

References

The following information has been placed on file in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. "Study of the Mutagenic Effects of Ammoniated Glycyrrhizin (71–1) by the Dominant Lethal Test in Rats," Stanford Research Institute, Menlo Park, CA, 1977.

2. "Testing for Potential Mutagens by Use of Unscheduled DNA Synthesis (UDS) in the Germ Cells of Male Mice," Division of ***54989** Biology, Oak Ridge National Laboratory, Oak Ridge, TN, 1982.

3. Bannister, B., R. Ginsburg, and J. Shneerson, "Cardiac Arrest due to Licorice-induced Hypokalemia," British Medical Journal, September 17, 1977, pp. 738–739.

4. Conn, J. W., D. R. Rovner, and E. I. Cohen, "Licorice-induced Pseudoaldosteronism," Journal of the American Medical Association, 205:80–84, 1968.

5. Cumming, A. M. M., J. J. Brown, A. F. Lever, K. Boddy, R. Fraser, P. L. Padfield, and J. I. S. Robertson, "Severe Hypokalemia with Paralysis Induced by Small Doses of Liquorice," Postgraduate Medical Journal, 56:526–529, 1980.

6. Epstein, M. D., E. A. Espiner, R. A. Donald, and H. Hughes, "Effect of Eating Licorice on the Renin-Angiotensin Aldosterone Axis in Normal Subjects," British Medical Journal, 1:488–490, 1977.

7. Miller, E., T. Michel, G. Ikeda, L. Garthoff, J. Peggins, and M. Khan, "Cardiovascular and Electrolyte Effects of Subchronic Administration of Glycyrrhizin and Salt in Minature Swine (Abstract)," Federation Proceedings, 40(3), Part I, 529, 1981.

8. Sundararm, M. B. M. and R. Swaminathan, "Total Body Potassium Depletion and Severe Myopathy due to Chronic Liquorice Ingestion," Postgraduate Medical Journal, 57:48–49, 1981.

9. Werner, S., K. Brismar, and S. Olsson, "Hyperprolactinemia and Licorice," The Lancet, February 10, 1979, p. 319.

10. Wood, C., "Literature Review of Toxicological Effects from Ammoniated Glycyrrhizin," attachment to comment submitted by Burditt and Calkins, Chicago, IL, dated October 15, 1979.

11. Capra, C., Fitoterapia, N. 4, p. 133, 1970. Translation supplied by Inverni Della Beffa as part of a comment dated July 13, 1979.

List of Subjects

21 CFR Part 182
Generally recognized as safe (GRAS) food ingredients, Spices and flavorings.

21 CFR Part 184
Direct food ingredients, Food ingredients, Generally recognized as safe (GRAS) food ingredients.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), it is proposed that Parts 182 and 184 be amended as follows:

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE
1. In Part 182:
21 CFR § 182.10

§ 182.10 [Amended]
a. In § 182.10 Spices and other natural seasonings and flavorings by removing the entries for “Glycyrrhiza” and “Licorice. ”
21 CFR § 182.20

§ 182.20 [Amended]
b. In § 182.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) by removing the entries for “Glycyrrhiza”, “Licorice,” and “Glycyrrhiza, ammoniated.”

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE
21 CFR § 184.1408
2. In Part 184, by adding new § 184.1408, to read as follows:
21 CFR § 184.1408

§ 184.1408 Licorice and licorice derivatives.
(a)(1) Licorice (glycyrrhiza) root is the dried and ground rhizone and root portions of Glycyrrhiza glabra or other species of Glycyrrhiza. Licorice extract is that portion of the licorice root that is, after maceration, extracted by boiling water. The extract can be further purified by filtration and by treatment with acids and ethyl alcohol. Licorice extract is sold as a liquid, paste (“block”), or spray-dried powder.

(a)(2) Ammoniated glycyrrhizin is prepared from the water extract of licorice root by acid precipitation followed by neutralization with dilute ammonia. Monoammonium glycyrrhizinate (C42 H61 O[FN16] H4 5H2 O, CAS Reg,. No. 1407–03–0) is prepared from ammoniated glycyrrhizin by solvent extraction and separation techniques.
(b) The ingredients shall meet the following specifications when analyzed:

(b)(1) Assay. The glycyrrhizin content of each flavoring ingredient shall be determined by the method in the Official Methods of Analysis of the Association of Official Analytical Chemists, 13th Ed., sec. 19.136, which is incorporated by reference. Copies

are available from the Association of Official Analytical; Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, DC 20044, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(b)(2) Ash. Not more than 9.5 percent for licorice, 2.5 percent for ammoniated glycyrrhizin, and 0.5 percent for monoammonium glycyrrhizonate on an anhydrous basis as determined by the method in the Food Chemicals Codex, 3d Ed. (1981), p. 466, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(b)(3) Acid insoluble ash. Not more than 2.5 percent for licorice on an anhydrous basis as determined by the method in the Food Chemicals Codex, 3d Ed. (1981), p. 466, which is incorporated by reference.

(b)(4) Heavy metals (as Pb). Not more than 40 parts per million as determined by method II in the Food Chemicals Codex, 3d Ed. (1981), p. 512, which is incorporated by reference.

(b)(5) Arsenic (As). Not more than 3 parts per million as determined by the method in the Food Chemicals Codex, 3d Ed. (1981), p. 464, which is incorporated by reference.
(c) In accordance with § 184.1(b)(2), these ingredients are used in food only within the following specific limitations:

Category of food	Maximum level in food [FN1]	Functional use
Baked goods, § 170.3(n)(1) of this chapter	0.05	Flavor enhancer, § 170.3(o)(11) of this chapter; or flavoring agent, § 170.3(o)(12) of this chapter.
Alcoholic beverages, § 170.3(n)(2) of this chapter	0.1	Flavor enhancer, § 170.3(o)(11) of this chapter; flavoring agent, § 170.3(o)(12) of this chapter; or surface-active agent, § 170.3(o)(29) of this chapter
Nonalcoholic beverages, § 170.3(n)(3) of this chapter	0.15	Do.
Chewing gum, § 170.3(n)(6) of this chapter	1.1	Flavor enhancer, § 170.3(o)(11) of this chapter; or flavoring agent, § 170.3(n)(12) of this chapter.
Hard candy, § 170.3(n)(25) of this chapter	16.0	Do.
Herbs and seasonings, § 170.3(n)(26) of this chapter	0.15	Do.
Plant protein products, § 170.3(n)(33) of this chapter	0.15	Do.
Soft candy, § 170.3(n)(38) of this chapter	3.1	Do.
Vitamin or mineral dietary supplements	0.5	Do.


```
All other foods except sugar
substitutes, § 170.3(n)(42) of
this chapter. The ingredient is
not permitted to be used as a
non-nutritive sweetener in sugar
substitutes ............................... 0.1 Do.
-------------------------------------------------------------------------------
1 Percent glycyrrhizin content of food, as served.
```

(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

Interested persons may, on or before February 6, 1984, submit to the Dockets Management Branch (address above), written comments regarding this tentative final rule. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the ***54990** heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 16, 1983.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 83–32646 Filed 12–7–83; 8:45 am]

BILLING CODE 4160–01–M